

Nonantibiotic measures for the prevention of Gram-positive infections

P. Eggimann¹ and D. Pittet²

¹Medical Intensive Care Unit, ²Infection Control Program, Department of Internal Medicine, University of Geneva Hospitals, Geneva, Switzerland

While Gram-negative bacteria remain a leading cause of nosocomial infections such as ventilator-associated pneumonia and catheter-associated urinary tract infections, Gram-positive cocci are now responsible for a large majority of surgical site and bloodstream infections. A shift has occurred during the last decade and multidrug-resistant micro-organisms have become predominant in most referral centers. Severe infections with Gram-positive micro-organisms such as methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci, penicillin-resistant *Streptococcus pneumoniae* and, more recently, glycopeptide intermediate *S. aureus* are now regularly reported to be associated with increased morbidity and represent a true health problem in many institutions. The importance of nonantimicrobial measures to prevent infections and further spread is reviewed in this paper. New evidence of the effectiveness of basic infection control measures that have been regarded of little importance during the last two decades by the exponential progress of technologically sophisticated medicine, is discussed.

Keywords bloodstream infection, educational programs, Gram-positive cocci, hand hygiene, nosocomial infection, prevention of infection

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INTRODUCTION

The Institute of Medicine in Washington recently estimated that preventable adverse events in the USA, including nosocomial infections (NI), are responsible for 44 000–98 000 deaths annually and represent a cost of \$17–29 billion [1]. Among these, NI now affect 5%–15% of hospitalized patients. Surgical site, urinary tract and pneumonia and bloodstream infections account for more than 80%, with Gram-positive cocci responsible for the majority of them. NI complicate 25%–50% of intensive care unit (ICU) stays [2]. Pneumonia related to mechanical ventilation, intra-abdominal infections following trauma or surgery, and bacteremias or sepsis related to intravascular devices account for more than 80% of these types of infections [3,4].

The proportion of infections caused by Gram-positive cocci has continuously increased over the past two decades [4–6]. This shift in the microbiology of micro-organisms responsible

for NI is also characterized by an irremediable rise in the proportion of resistant organisms [7]. Recent data from the National Nosocomial Infection Surveillance (NNIS) system show an increase in the percentage of enterococcal isolates resistant to vancomycin from 0.5% in 1989 to 22% in 1997. During the same period, the proportions of MRSA and of methicillin-resistant coagulase-negative staphylococci have increased from 29% to 42%, and from 75% to 86%, respectively [8]. Continuing evidence strongly suggests that this may be due in a large part to antibiotic overuse, antimicrobials are not only too generously used in human care but, also, in animal rearing [9–11]. Some experts suggest that this evolution may already place us in a health situation comparable with the preantibiotic era [12–15].

Accordingly, measures targeted at the prevention of NI should become a priority target of our healthcare management. Infection control includes epidemiological surveillance of NI and preventive measures. This includes general measures such as isolation precautions and restriction of antibiotic use, which will not be discussed in this paper, and more specific measures targeted at the prevention of specific infections [15–18]. The concept of standard and transmission-based precautions, with special emphasis on hand-hygiene measures, will be discussed and the prevention of vascular-access-related infections will

Corresponding author and reprint requests: D. Pittet, Infection Control Program, Department of Internal Medicine, Geneva University Hospitals, 24 rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland
Tel: +41 22 372 9828
Fax: +41 22 372 3987
E-mail: didier.pittet@hcuge.ch, philippe.eggimann@hcuge.ch

illustrate the positive impact of behavioral changes on the reduction of NI rates.

SURVEILLANCE OF NI

Surveillance of NI was recognized to be a major component of infection control late in the late 1970s. The Study on Efficacy of Nosocomial Infection Control (SENIC) showed that NI rates decreased 32% on average in hospitals where surveillance programs were implemented, as compared with an increase of 18% in other institutions over a 5-year period [19]. Only 8% of the institutions included in this survey had an established infection control program, but this proportion rapidly increased as they were imposed as an important criteria for hospital accreditation [20]. These programs are less widespread and formally established in Europe than in the USA, but they have also been introduced progressively in most countries [21,22].

A planned epidemiological surveillance system with regular feedback of NI rates is the cornerstone of infection control programs. The continuous collection, tabulation, analysis and dissemination of information on the occurrence of NI in a specified ward and/or hospital can be conducted in several ways [23]. Total surveillance includes meticulous collection of clinical and microbiological data for all hospitalized patients. This technique is labor-intensive, time-consuming and not always feasible on a practical basis [24]. Target-oriented surveillance is restricted to specific objectives, such as the control of the spread of resistant organisms or the reduction of the incidence of a defined NI. Infection-specific surveillance is

limited to particular types of infections such as outbreaks, or to specific laboratory data. Unfortunately, the sensitivity of the methods that may be used to collect the information is inversely correlated with the time investment required (Table 1) [19,20,25–27].

In practical terms, a combined approach allows an optimal use of resources [27]. Continuous monitoring of different infections or micro-organisms is mandatory to detect outbreaks that require both specific and emergency measures [28]. Surveillance of defined infections in particular wards or units may be useful for particular epidemiological profiles and may help to design targeted programs to reduce NI [29–32].

Computerized systems may be extremely helpful to facilitate the rapid identification of specific problems. For example, we implemented a fully computerized automatic alert system to identify at the time of admission any patient in whom the microbiology laboratory has previously identified MRSA [28].

CONTROL AND PREVENTION

Preventive measures are the most effective way to control NI, and consensus conference and expert panels have established numerous guidelines both in the USA and in European countries [9,18,33–35].

Isolation guidelines

Transmission of infection occurs by the spread of micro-organisms from a pathogenic source through a susceptible

Table 1 Sensitivity and time requirement of selected methods for surveillance of NI

Methods for surveillance	Description of the methods	Sensitivity ^a	Time required (h/week/500 beds) ^a
Patient chart review	Complete review of all patients' charts of a considered ward/hospital, including microbiological data from the laboratory	75%–95%	36–54
Laboratory data	Identification on laboratory reports of all patients of a considered ward/hospital with positive microbiological cultures	75%–90%	23
Ward documents review	Identification of patients of a considered ward suspected or prone to be at risk of developing a NI	75%–95%	14–22
Temperature	Identification of all patients with a body temperature $\geq 37.8^{\circ}\text{C}$	10%–60%	8
Antibiotics	Review of data on patients receiving antibiotics only	60%	14
Temperature and antibiotics	Review of all patients with a body temperature $\geq 37.8^{\circ}\text{C}$ and receiving antibiotics	70%	13
Readmission	Review of data of all patients readmitted only	5%–10%	?
Autopsy	Review of data all autopsied patients only	5%–10%	1

^aAdapted from [19,20,25–27].

host. Some hospital wards where highly infection-prone patients are present are at particularly high risk for cross-transmission of nosocomial pathogens. Indeed, more than 50% of those admitted in ICUs harbor micro-organisms that may serve as a reservoir for subsequent endemic and epidemic spread [36–38]. However, patient-to-patient transmission occurs only infrequently and it is the hands of healthcare workers (HCWs) that are the most significant means of transmission.

Isolation guidelines enable HCWs to identify patients who need to be isolated and to choose the appropriate measures. The Centers for Disease Control and Prevention (CDC) first formalized modern guidelines for isolation in hospitals in the early 1970s. These were subsequently modified several times to address emerging problems in infectious diseases. These recommendations are complex and somewhat difficult to apply in the context of daily practice. The last version issued from the CDC and the Hospital Infection Control Practice Advisory Committee (HICPAC) in 1996 defined two levels of bedside transmission prevention: standard precautions, applied to all patients, and transmission-based precautions, applied to patients with documented or suspected colonization and infection with specific micro-organisms [18].

Standard precautions

Standard precautions encompass the concept that any patient should be approached in a manner that would minimize the risk of 'micro-organisms' transmission. They apply to blood and all body fluids (secretions and excretions except sweat) visibly bloody or not, as well as all contact with nonintact skin and/or mucous membranes (Table 2). These recommendations are based on solid rationale and on extensive evidence that routine adherence to them decreases the risk of infection transmission.

Transmission precautions

This level of precaution applies to selected patients with suspected or confirmed infection that predictably places others at risk of acquiring this infection. Specific isolation precautions are required according to the three major routes of infection transmission, which are designated as contact, droplet and airborne (Table 3).

Contact precautions Contact transmission is the most important route for infection transmission in the hospital. Transmission occurs via physical contact with skin, mostly from contaminated or colonized hands of HCWs to patients. Physical contact also applies to contact with contaminated surfaces or

Table 2 Standard precautions^a

Measures	Field of systematic application of the measures
Hand hygiene	Hand disinfection: – After contact with blood, body fluids, secretions, excretions, contaminated items – Immediately before gloving and after glove removal – Between any contacts with any patients Hand washing: – For macroscopically dirty hands before and/after any care
Gloves	For anticipated contact: – With blood, body fluids, secretions, excretions, contaminated items – With mucous membranes, and/or nonintact skin Importantly: – Hands have to be systematically disinfected after glove removal
Mask, eye protection, and face shield	To protect mucous membranes of the eyes, nose and mouth during procedures and patient-care activities likely to generate splashes or spray of blood, body fluids, secretions and excretions
Gowns	To protect skin and prevent soiling of clothing during procedures and patient-care activities likely to generate splashes or spray of blood, body fluids, secretions and excretions Impermeable gown should be used when appropriate

^aAdapted from HICPAC guidelines [18]. Available on-line at: <http://www.cdc.gov/ncidod/hip/isolat/isolat.htm>

Table 3 Transmission-based precautions^a**Contact precautions**

Apply for patients known or suspected to have diseases transmitted by direct physical contact or contact with items in the patient's environment

Infection/colonization with multidrug-resistant bacteria ^b	According to infection control policy and guidelines at the hospital ^c ;
Enteric infections	<i>Clostridium difficile</i> <i>Escherichia coli</i> O157:H7 <i>Shigella</i> spp. Hepatitis A virus Rotavirus
Respiratory infections in children	Respiratory syncytial virus Parainfluenza virus Enteroviral infections
Highly contagious skin infections	Neonatal or mucocutaneous Herpes simplex Disseminated zoster† Impetigo Staphylococcal furunculosis in infants and children Uncovered abscesses, cellulitis, decubitus Pediculosis and scabies
Viral hemorrhagic conjunctivitis	
Viral hemorrhagic fevers ^d	Lassa, Ebola, Marburg viruses
Systemic syndromes	<i>Neisseria meningitidis</i> infections <i>Haemophilus influenzae</i> meningitis GAS ^d scarlet fever, toxic shock syndrome

Droplet precautions

Apply for patients known or suspected to have diseases transmitted by large droplets

Systemic syndromes	<i>Neisseria meningitidis</i> infections <i>Haemophilus influenzae</i> meningitis GAS ^d scarlet fever, toxic shock syndrome
Respiratory infections	<i>Haemophilus influenzae</i> , pneumonia, epiglottitis GAS ^d pharyngitis <i>Mycoplasma pneumoniae</i> Pertussis
Serious viral infections	Adenovirus Influenza Mumps Parvovirus B19 Rubella
Respiratory infections	Measles Varicella and disseminated zoster Tuberculosis, pulmonary and laryngeal

Airborne precautions

Apply for patients known or suspected to have diseases transmitted by airborne particles

Respiratory infections	Measles Varicella and disseminated zoster Tuberculosis, pulmonary and laryngeal
Viral hemorrhagic fevers ^d	Lassa, Ebola, Marburg viruses

^aA nonexhaustive list, adapted from the HICPAC guidelines [18].

^bExtended-spectrum β -lactamase producing enterobacteriae (ESBL); multiresistant *Pseudomonas aeruginosa*; multiresistant *Enterobacter cloacae*.

^cSee section on Antibiotic-resistant bacteria.

^dGroup A streptococci.

instruments such as stethoscopes, blood-pressure cuffs or other instruments of patient care. In addition to standard precautions, contact precautions prevent the transmission of micro-organisms of epidemiological importance, including methicillin-resistant *S. aureus* (MRSA), extended-spectrum β -lactamase-producing Gram-negative bacteria (ESBLs), vancomycin-resistant enterococci (VRE) and *Clostridium difficile*. Patients with suspected or confirmed infection should be placed in a private room or cohorted with other patients infected by the same organism. HCWs should wear gloves and a gown for any contact, which should be removed before leaving the room and followed by systematic hand disinfection. Patient-care devices, including stethoscopes and blood pressure cuffs, should not be used for other patients without rigorous cleaning and disinfection according to the hospital policy.

Droplet precautions Droplet transmission occurs when respiratory particles (larger than 5 μm in size) containing infecting micro-organisms (produced during coughing, sneezing and talking, or during invasive procedures such as bronchoscopy and suctioning) are subsequently deposited on the mucous membranes of the host's eye, nose or mouth. A close contact of less than 1 m is necessary for transmission to occur since respiratory droplets usually only travel short distances. In addition to standard precautions, droplet precautions prevent the transmission of micro-organisms such as *Haemophilus influenzae* type b, meningococci, multidrug-resistant pneumococci or any other multidrug-resistant organisms in the respiratory tract (MRSA; ESBLs Gram-negative bacteria), pharyngeal diphtheria, *Mycoplasma pneumoniae* and some viral diseases. Accordingly, when working within 1 m of the patient a mask is recommended. Patients have to be placed in a private room or cohorted with another patient infected by the same organism. Special air handling and ventilation are not necessary, and the door may remain open. When these measures are not possible, a spatial separation of at least 1 m between the patient and other patients or visitors is mandatory.

Airborne precautions Airborne transmission occurs when infectious droplet nuclei or contaminated dust particles are inhaled. Droplet nuclei are less than 5 μm in size and can remain suspended in the air for long periods and travel long distances; therefore special air handling and ventilation are required to prevent transmission [18]. The most frequent indications include pulmonary and laryngeal tuberculosis, varicella and disseminated zoster, acute viral hemorrhagic fever, or measles. Patients should be placed in a private room with negative air pressure in relation to the surrounding area with at least six air changes per hour and an appropriate discharge of filtrated air before it is circulated to other areas in the hospital [39]. The door of the room should be kept closed.

When an isolation room with an anteroom is used, the two doors should not be opened at the same time. When such isolation rooms are not available, the patient should be placed in a private room or cohorted with another patient infected by the same organism. In these situations, a consultation with the infection control team is advised. Airborne precautions require respiratory protection with high-efficiency masks (dust-masks) that have been approved by the National Institute for Occupational Safety and Health (N-95 standard) to be worn by any HCWs or visitors [40,41]. This has also to be applied to the patient during transport and/or movements outside his/her isolation room.

Hand hygiene measures

Hand hygiene before and after patient contact remains the most important component of the concept of standard precautions presented above [42,43]. Endemic transmission of exogenous staphylococci and other potential pathogens by the hands of HCWs is well documented [36–38,44,45]. Goldman *et al* reported that Gram-negative bacilli were found to be present on the hands of 75% of neonatal ICU personnel [46]. A recent report from the National Epidemiology of Mycoses Survey with surveillance cultures systematically performed on the hands of HCWs from 13 ICUs, showed that 33% (18%–58%) in adult ICUs and 29% (8%–62%) in pediatric ICUs were positive for *Candida* spp. over an 18-month period [47]. We recently demonstrated that bacterial contamination of the hands increases linearly with time on ungloved hands during patient care (16 colony-forming units [CFUs] per minute; CI, 11–25 CFU/min). Higher contamination was documented with direct patient contact such as respiratory care, handling of body fluid secretions and rupture in the sequence of patient care [48].

Updated guidelines for hand washing and/or hand disinfection were published by the Healthcare Infection Control Practices Advisory Committee (HICPC) in 1995 (<http://www.cdc.gov/ncidod/hip/sterile/sterile.htm>) [49]. Hand hygiene is the term used for hand-cleansing methods. This includes hand washing with plain soap and water alone, or with an antimicrobial soap, hand-rub with a waterless alcohol-based compound, and surgical hand scrub [49]. Hand disinfection refers to any action where an antiseptic solution, either medicated soap or alcohol, is used to clean hands. Hand washing procedures mechanically remove dirt (extraneous substances, sweat, skin lipids, epithelial debris, etc.) and adhering skin bacteria [18,42]. The efficacy of hand-hygiene methods is expressed as the difference in \log_{10} CFU before and after the procedure. For traditional hand washing with soap and water, the main reduction of transient flora is achieved within the first 30 s (0.6–1.1 logs at 15 s and 1.8–2.8 logs at 30 s).

Extending the procedure results in reductions of 2.7–3.0 logs, 3.3 logs and 3.7 logs after 1, 2 and 4 min respectively [50].

However, low level compliance with hand hygiene has been systematically reported, particularly in ICUs, where it does not exceed 40% [31,51–53]. Several reasons have been suggested for such a low level of compliance, including lack of priority over other required procedures, insufficient time, inconvenient placement of hand-washing facilities, allergy or intolerance to hand-hygiene solutions and lack of leadership from senior medical staff [52,54–56]. For example, it was estimated that in the ICU almost two-thirds of work time could be theoretically required for optimal adherence to infection control guidelines on hand-hygiene practice [57]. Accordingly, we recently reported that compliance was inversely proportional to the number of opportunities per hour of patient care [31]. In addition, those who do wash frequently and vigorously risk skin damage that, ironically, results in the shedding of more organisms into the environment [58]. Attempts to improve compliance with hand hygiene have been associated with some improvement [59,60]. Experience with alcohol-based hand-rubs suggested that hand disinfection reduces hand contamination more than hand washing [61]. Alcohol-based waterless hand-rub consists in applying a small amount (3–5 mL) of a fast-acting antiseptic preparation on both hands that then have to be rubbed together for 10–15 s [49]. The reduction in transient flora achieved after 30 s is 3.4–3.7 logs for alcohol (1-min hand-rub: 4.0–5.8 logs). Similar reductions are achieved with chlorhexidine gluconate, but with a prolonged effect [62]. In a study already mentioned, we have found that the method of hand cleansing before care had a significant impact [48]. A multivariate analysis revealed that HCWs who washed their hands with plain soap had an excess of 52 CFU on their fingertips, compared with those who used a hand disinfection system using an alcohol-based solution (70%) with an antimicrobial agent (chlorhexidine 0.5%).

In a study published by Doebbeling *et al* a chlorhexidine-distributing system reduced the rate of NI more effectively than one using alcohol and soap. This improvement was essentially explained by a better compliance with hand-hygiene instructions when chlorhexidine was used [59]. This was also the case in a French medical ICU where the increase in compliance to hand-hygiene measures from 42.4% to 60.9% was essentially attributed to the availability of an alcohol solution for hand-rubs [53]. Unfortunately, the effect of this intervention was not sustained and compliance decreased over a 3-month period from 60.9% to 51.3%. At our institution, the promotion of an elementary bedside hand-disinfection technique by an hospital-wide campaign, resulted in a sustained improvement in compliance with hand hygiene from 48% to 66% over 4 years. During the same period, the

prevalence of overall NI and MRSA transmission decreased both from 16.9% to 9.9% and from 2.16 to 0.93 episodes per 10 000 patient-days respectively. Taking the hypothesis that only 25% of the reduction in the infection rates could be attributed to the improved compliance in hand-hygiene practice, this intervention might have prevented more than 900 NI and thus was largely cost-effective [63].

Behavioral changes may have played a key role in the success of this intervention, based on a multimodal and multidisciplinary approach including communication and education tools such as 'Talking Walls' (widely exhibited cartoon posters available at www.hopisafe.ch), active participation and positive feedback at both individual and institutional levels, and systematic involvement of institutional leaders [64–67].

Specific measures targeted at reduction of vascular-access infection

Catheter-related infections (CRIs) include colonization of the device, skin exit-site infection and device-related bloodstream infection [68–74]. They represented 12% of all NI reported in 10 038 patients from 1417 ICUs in the European Prevalence of Infection in Intensive Care (EPIC) study [75]. The NNIS system reported that most nosocomial bloodstream infections are related to intravascular access, with rates substantially higher among patients with central venous catheters (CVCs) than among those with peripheral lines [3,4]. Rates of bloodstream infections range between 2.8 and 12.8 episodes per 1000 catheter-days and may have a significant impact on patient morbidity and hospital costs in ICUs [4,76–79]. Most micro-organisms implicated in CRIs arise from the skin flora and Gram-positive cocci are responsible for at least two-thirds of infections [3,70,80–83]. More than 50% of patients admitted to ICUs are already colonized at the time of admission, with the organism responsible for subsequent infection [47].

Accordingly, the prevention of CRIs relies on a careful control of all the factors associated with the colonization of vascular accesses by micro-organisms; evidence-based guidelines and preventive measures have been published by the Hospital Infections Control Practices Advisory Committee [84]. This topic was also recently extensively reviewed elsewhere [85,86]. As for hand-hygiene measures, low-level compliance with the recommendations is regularly reported. However, recent data suggested that behavioral changes induced by educational-based programs might have a significant impact on the reduction of infection rates.

Sherertz *et al* recently reported that an educational program of physicians-in-training could also decrease the risk of CRIs. A 1-day course on infection control practices and on

Table 4 Specific recommendations for the prevention of catheter-related infections^a

Type of action	Recommendation
Material preparation	Material has to be prepared according to a detailed list (hospital policy) to avoid interruption during insertion
Patient installation	Precise recommendations for the placing of patients and devices to guarantee an optimal access to the insertion site The presence of a nurse to assist the physician is strongly recommended
Insertion	Specific training for ICU physicians and detailed written guidelines for the staff are recommended
Skin preparation:	Hair-cutting instead of shaving. Skin cleansing with surgical swab
Skin antisepsis:	Alcohol-based (70%, v/v) solution with chlorhexidine gluconate (0.5%), with 2 min drying time before insertion
Barrier precautions:	Maximal sterile barriers: sterile gown, gloves and large drapes; cap; surgical mask ^b
Insertion technique:	Consider systematic promotion of subclavian site for CVCs and wrist vein for short lines
Dressing	Discard occlusive devices and promote dry gauze-based dressing occluded with porous adhesive band Replace any dressing every 72 h except for the first dressing after catheter insertion
Replacement	Administration sets and devices: replacement at 72-h intervals Lines for lipid emulsion: replacement at 24-h intervals Lines for blood product: remove these lines immediately after use
General handling	Opening of hub: on antiseptic-impregnated pads after hand disinfection General measure: use new caps after any opening of the hubs
Device removal	Peripheral line: remove them after 72 h systematically Central line: remove them as clinically indicated, no routine replacement Any vascular access: prompt removal if not absolutely necessary Clinical sepsis: guidewire exchange if unexplained by a another potential source of infection
Hand hygiene	Systematic application of the requirements of standard precautions (Table 3)

^aAdapted from [32,84].^bFor the insertion of all but peripheral lines [90].

procedures of vascular access insertion was shown to reduce the infection rate by 27%, from 3.3 to 2.4 per 1000 CVC-days [87]. We recently completed a study to evaluate the impact of a global strategy targeted at the reduction of CRIs in 3154 critically ill patients consecutively admitted to a medical ICU. Specific guidelines included in the global strategy implemented through an educational program targeted at vascular access care are discussed in the preceding sections and are presented in Table 4. The program consisted of slide-show-based educational sessions and bedside training of all staff, including nurses. Following the introduction of the program, the incidence-density of exit-site catheter infection decreased by 64%, and that of bloodstream infection by 67%. Although the over-all exposure to CVC did not significantly differ between the control and the intervention periods (median duration, 4 days, $P=0.94$), the incidence-density of bloodstream infection markedly decreased from 22.9 to 6.2 episodes per 1000 CVC-days due to a reduced incidence of both microbiologically documented infection (from 6.6 to 2.3 episodes per 1000 CVC-days) and clinical sepsis (from 16.3 to 3.9 episodes per 1000 CVC-days). Overall, the incidence-density of NI was reduced by 35% (from 52.4 to 34.0 episodes per 1000 patient-days), corresponding to the prevention of more than 75 NI over an 8-month period, including at least 30 primary bloodstream infections and 25 vascular-access related infections. It was estimated that it would also correspond to the annual salary of three full-time infection control nurses [32]. In addition, the impact in terms of reduction of NI in these two

studies was largely superior to that expected with the use of antimicrobial/antiseptic-coated catheters [88,89].

As for the improvement in hand hygiene discussed below [63], these observations indicate that behavioural changes may have played a key role in the success of educational programs, which were based on multimodal and multidisciplinary approaches including communication and education tools, active participation and feedback, and systematic involvement of the leaders [64,66].

CONCLUSION

The prevention of NI, including those related to Gram-positive micro-organisms, must include a series of bedside measures that have to be implemented under the supervision of infection control teams. They must become one of the priority targets of a multidisciplinary approach emphasizing quality-of-care improvement.

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